Quality of Life Subcommittee
Oncologic Drugs Advisory Committee
February 10, 2000

Introduction

In 1985, the Oncologic Drugs Advisory Committee recommended that beneficial effects on quality of life (QOL) endpoints could serve as the basis for approval of new oncology drugs. Therefore, from a regulatory standpoint, for drugs that do not have an impact on survival, demonstration of a favorable effect on QOL would be considered more compelling than improvements in other measures, such as objective tumor response rate.

Increasingly, QOL endpoints are being incorporated into randomized, controlled clinical trials in oncology. Pharmaceutical companies are seeking novel approaches with which to establish the benefits of drug treatment and to differentiate their products from other marketed products. Health care providers and cancer patients need definitive information when choosing among potentially toxic therapies.

To date, most oncology drug approvals have been based on traditional efficacy endpoints such as survival or tumor response rate. The Quality of Life Subcommittee, comprised of several experts in the field of QOL research as well as members of the Oncologic Drugs Advisory Committee, has been convened to serve as a public scientific forum for discussion of issues related to the use of QOL endpoints for approval of new oncology drugs. These issues include but are not limited to the challenges of QOL assessment, approaches to the statistical analysis of data, and clinical interpretation of results. Some of the points that may be considered by the Quality of Life Subcommittee at its first meeting are described below.

Points to Consider

- **Definitions**

Most experts agree that health-related QOL is a multidimensional construct that represents the patient's perspective on valued aspects of health and functioning. A spectrum of instruments have been developed for the evaluation of cancer patients, ranging from global QOL scales, to disease- or symptom-specific scales, to ad hoc instruments that are specific to a single study. Often, more than one scale may be used to assess QOL in a trial. Understanding the relative strengths and weaknesses of each type of scale is critical to developing a rational approach to selecting scales for particular disease settings, patient populations, study designs, etc.

The Division of Oncology Drug Products at FDA has valued improvement in tumor-related symptoms (or prolongation in time to symptomatic progression) as evidence of clinical benefit for patients in oncology drug trials. This is based on the assumption that symptom improvement would be sensitive to the effects of drug therapy, and hence, clinically meaningful to patients. Historically, symptomatic improvement has been

difficult to demonstrate in oncology drug trials unless sufficient numbers of symptomatic patients are enrolled and carefully assessed over time. When feasible, serious efforts to enrich trials with symptomatic patients should be entertained.

- **Clinical Interpretation**

Ideally, substantive validation of an instrument would be performed prior to its use in the principal trials that will be submitted in support of approval of a new oncology drug. For the principal studies then, the study protocol(s) should prospectively specify the magnitude of change in scores that would constitute meaningful patient benefit.

Often, a battery of questions is asked and summary scores are calculated. Given the possibility that positive outcomes will not be observed for all questions, improvement in some items and worsening in others could occur. Demonstration of seemingly conflicting outcomes would be problematic and presumably less persuasive from a regulatory point of view.

- **Data Analysis**

Careful planning at the design stage can substantially facilitate the analysis of QOL data. The review of regulatory submissions can be seriously hampered by sizable amounts of missing data, particularly baseline data, which can render an analysis meaningless, and by improper imputation for missing values. Development of a missing value strategy is highly desirable, particularly in trials of advanced cancer patients who are more likely to drop out of studies early due to disease progression or drug toxicity. In the past, the Division of Oncology Drug Products has used longitudinal approaches to assess a variety of outcomes over time, including scores of pain intensity, analgesic use, and Karnofsky performance status.

Other difficulties arise when there is a failure to correct for multiple comparisons to baseline and/or multiple endpoints. Ideally, prior to study initiation, and definitely prior to study unblinding (if applicable), a detailed statistical analysis plan should be developed that addresses potential sources of type I error. Failure to adjust for the effects of concomitant medications that could affect QOL outcomes, such as use of antidepressants, is also problematic and should be avoided.

Conclusions

Interest in QOL outcomes in oncology drug trials has been growing and will continue to grow. Inclusion of QOL endpoints in randomized, controlled trials will likely be the rule rather than the exception in the foreseeable future. Trials incorporating QOL endpoints will be evaluated on the basis of how well they meet prospectively defined objectives. Given the unique challenges that face the pharmaceutical industry and other sponsors of clinical trials, the Division of Oncology Drug Products welcomes the advice and recommendations of the Quality of Life Subcommittee regarding the use of QOL endpoints in trials submitted for approval of new oncology drugs.